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REVIEW TOPIC OF THE WEEK

# Aspirin Therapy in Primary Cardiovascular Disease Prevention

## A Position Paper of the European Society of Cardiology Working Group on Thrombosis

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**ABSTRACT**

Although the use of oral anticoagulants (vitamin K antagonists) has been abandoned in primary cardiovascular prevention due to lack of a favorable benefit-to-risk ratio, the indications for aspirin use in this setting continue to be a source of major debate, with major international guidelines providing conflicting recommendations. Here, we review the evidence in favor and against aspirin therapy in primary prevention based on the evidence accumulated so far, including recent data linking aspirin with cancer protection. While awaiting the results of several ongoing studies, we argue for a pragmatic approach to using low-dose aspirin in primary cardiovascular prevention and suggest its use in patients at high cardiovascular risk, defined as ≥2 major cardiovascular events (death, myocardial infarction, or stroke) projected per 100 person-years, who are not at increased risk of bleeding. (J Am Coll Cardiol 2014;64:319–27) © 2014 by the American College of Cardiology Foundation. Open access under CC BY-NC-ND license.

*"Natura non facit saltus."*
*(Nature does not make jumps.)*
—Gottfried Leibniz (1)

The recognition that thrombosis plays an important role in acute cardiovascular disease (CVD) (2,3) has resulted in a large number of clinical trials on the effectiveness of antithrombotic drugs in CVD prevention. The benefit of antiplatelet drugs (aspirin and $P2Y_{12}$ inhibitors) in reducing mortality and/or new cardiovascular events in patients with prior CVD (secondary prevention) with an acceptable risk of bleeding has been clearly shown (4,5). However, in patients without prior CVD (primary prevention), the indication for antithrombotic drugs is still unclear. In this population, aspirin—the only antithrombotic drug studied in sufficiently large patient cohorts—produces a statistically significant reduction in the risk of a first myocardial infarction (MI), but increases the risk of both gastrointestinal

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**ABBREVIATIONS AND ACRONYMS**

**CHD** = coronary heart disease

**CI** = confidence interval

**CVD** = cardiovascular disease

**GI** = gastrointestinal

**MI** = myocardial infarction

**PAD** = periphery arterial disease

**RCT** = randomized controlled trial

(GI) bleeding and hemorrhagic stroke (6). As a result, guidelines and other expert opinions differ substantially in their recommendations for primary prevention, reflecting the uncertainty of a precise risk/benefit ratio in this population.

This document, produced by a committee appointed by the European Society of Cardiology (ESC) Working Group on Thrombosis, reviews and discusses the most up-to-date evidence for the safety and efficacy of aspirin use in primary CVD prevention, with the main aim of issuing practical recommendations.

## METHODS

We searched the electronic PubMed database for randomized controlled trials (RCTs) or meta-analyses of RCTs using the following terms: anticoagulants OR aspirin OR antiplatelet drugs AND primary prevention AND coronary heart disease OR cardiovascular disease OR coronary artery disease OR peripheral arterial disease (PAD) OR cancer OR all-cause mortality. The last literature searches were performed on February 28, 2014. The authors critically evaluated the evidence, with an assessment of the risk/benefit ratio. The strength of recommendation and level of evidence of particular treatment options were weighed and graded according to the ESC system (7).

## ASSESSING BASELINE RISK

In primary CVD prevention, in which the risk of developing atherothrombotic events is generally low, it is essential to estimate the individual baseline risk of such events and carefully balance this against the risk of adverse outcomes related to therapy. Commonly-used tools to assess baseline risk are the Framingham coronary heart disease (CHD) risk score (8), the recently released American College of Cardiology/American Heart Association (AHA/ACC) Task Force risk equations (9), ESC's SCORE (Systematic Coronary Risk Evaluation), or national risk charts. Some tools assess the risk of cardiovascular death, whereas others assess all major cardiovascular events. The Framingham CHD risk score predicts the 10-year risk of developing a coronary event (composite of MI and coronary death), and individuals are categorized as low (<10%), moderate (10% to 20%), or high (>20%) risk. Conversely, the SCORE system, recommended in the ESC guidelines (7), estimates the 10-year risk of a fatal atherosclerotic event: individuals are considered at low risk with a SCORE <1%, at moderate risk with a SCORE ≥1% and <5%, at high risk with a SCORE ≥5% and <10%, and at very high risk with a SCORE ≥10% (7). Clearly, the risk of total fatal and nonfatal events is higher than that of fatal events only. At a 5% risk of fatal events, the total event risk is approximately 15% (7). This 3-fold multiplier is somewhat smaller in the elderly, in whom a first event is more likely to be fatal.

## ASPIRIN IN PRIMARY CVD PREVENTION

The only antithrombotic drugs investigated for primary CVD prevention are vitamin K antagonists, which were investigated in only 1 trial and are currently abandoned (Online Appendix), and acetyl salicylic acid (aspirin). Aspirin has been studied in 9 large-scale RCTs (10–18), including more than 100,000 participants (**Table 1**, Online Appendix).

**META-ANALYSES OF PRIMARY CVD PREVENTION TRIALS WITH ASPIRIN.** The meta-analysis carried out by the ATT (Anti-Thrombotic Trialists) Collaboration in 2009 (6) included the first 6 primary prevention trials (10–15) (n = 95,000) and demonstrated that, over a 10-year period, aspirin therapy was associated with 6 fewer MIs per 1,000 low-risk persons treated (5% CHD risk at 10 years according to the Framingham risk categories). For persons at moderate (15%) and high (25%) CHD risk, aspirin led to a reduction of 19 and 31 MIs per 1,000 patients treated, respectively (8). The downside was that the risk of bleeding events was also higher as a function of cardiovascular risk. Thus, the overall reduction of MIs was almost balanced by the increase in bleeding events throughout baseline risk categories. Aspirin therapy did not seem to have an effect on stroke occurrence. With respect to mortality, there was a small protective effect of aspirin therapy, with 0 to 6 fewer deaths per 1,000 persons treated over 10 years. This protective effect on mortality was found to be of similar magnitude in persons at low

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**TABLE 1 Characteristics of Individual Trials of Aspirin in Primary Prevention**

| Trial, Year | Participants | Male, % | Mean Age, yrs | Aspirin Dose, mg | Duration of Follow-Up, yrs* | Primary Endpoint |
|---|---|---|---|---|---|---|
| BDT, 1988 | 5,139 | 100 | 63.6 | 500 or 300 daily | 6.0 | MI, stroke, or CV death |
| PHS, 1989 | 22,071 | 100 | 53.8 | 325 alternate day | 5.02 | MI, stroke, or CV death |
| HOT, 1998 | 18,790 | 53 | 61.5 | 75 daily | 3.8 | Major CV events |
| TPT, 1998 | 5,085 | 100 | 57.5 | 75 daily | 6.4 | Major coronary event |
| PPP, 2001 | 4,495 | 42 | 64.4 | 100 daily | 3.6 | MI, stroke, or CV death |
| WHS, 2005 | 39,876 | 0 | 54.6 | 100 alternate day | 10.1 | MI, stroke, or CV death |
| POPADAD, 2008 | 1,276 | 44 | 60.3 | 100 daily | 6.7 | CV death, MI, stroke, or amputation |
| JPAD, 2008 | 2,539 | 55 | 64.5 | 81 or 100 daily | 4.37 | Any atherosclerotic event |
| AAA, 2010 | 3,350 | 28 | 61.6 | 100 daily | 8.2 | Fatal or nonfatal coronary event, stroke, or revascularization |

*Duration of follow-up represents median follow-up for POPADAD and JPAD, mean follow-up for the other trials.

AAA = Aspirin for Asymptomatic Atherosclerosis; BDT = British Doctors Trial; CV = cardiovascular; HOT = Hypertension Optimal Treatment; JPAD = Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes; MI = myocardial infarction; PHS = Physicians Health Study; POPADAD = Prevention of Progression of Arterial Disease and Diabetes; PPP = Primary Prevention Project; TPT = Thrombosis Prevention Trial; WHS = Women's Health Study.

and at moderate-to-high risk for atherothrombotic events. Since bleeding risk appeared to be strongly related to the ischemic risk, the benefit of aspirin was judged to be overshadowed by the bleeding hazard. If aspirin were to be combined with other agents that would halve the risk of a major ischemic event, such as statins (19), the potential benefit of aspirin would be almost completely abolished.

Four additional meta-analyses have recently been performed by other groups, and published in 2011 to 2012 (20–23). In all of them, 3 additional trials were included: the JPAD (Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes), POPADAD (Prevention of Progression of Arterial Disease and Diabetes), and AAA (Aspirin for Asymptomatic Atherosclerosis) trials (16–18) (**Table 1**). These trials were somewhat nonhomogeneous with the previous ones, as they included individuals who, although asymptomatic, were at higher risk because of pre-existing diabetes, asymptomatic PAD, or both. In these meta-analyses, all-cause—but not vascular—mortality was slightly but consistently reduced, reiterating a risk ratio of 0.94 with uniform confidence limits (0.88 to 1.00), but without reaching formal significance. These figures compare well with those of the ATT meta-analysis (confidence limits: 0.88 to 1.02) (6). The claim for a significant reduction of mortality is not formally justified by the data and is possibly misleading (24,25).

In patients with asymptomatic PAD, a recent systematic review (26) confirmed that no differences were observed between aspirin and placebo for total and vascular mortality, MI, and stroke. In abdominal aortic aneurysms, a recent Cochrane systematic review (27) on pharmacological prevention of cardiovascular events did not include studies with antiplatelet agents, because any eligible studies failed to pass the quality assessment phase. Thus, there is no proof that, in asymptomatic PAD or asymptomatic aortic aneurysms alone, the use of aspirin confers an advantage over not using aspirin in CVD prevention.

**ADVERSE EVENTS WITH ASPIRIN.** The most common adverse effect associated with aspirin is bleeding. The meta-analysis by the ATT Collaboration found that allocation to aspirin increased major GI and other extracranial bleeds (defined "as a bleed requiring transfusion or resulting in death") by about 50% (0.10%/year vs. 0.07%/year; risk ratio: 1.54 [95% CI: 1.30 to 1.82], $p < 0.0001$) (6). Recently, it has been emphasized that the bleeding risk is higher in individuals at higher cardiovascular risk over 10 years. Compared with placebo, this high-risk population would experience 22 more bleeds per 1,000 persons treated with aspirin versus 4 more bleeds per 1,000 persons treated with aspirin in the low-risk population (8).

Aspirin also increases the risk of hemorrhagic stroke. A meta-analysis of 16 placebo-controlled RCTs, comprising a total of 55,462 patients, showed that treatment with aspirin was associated with a relative risk of hemorrhagic stroke of 1.84 ($p < 0.001$) (28). In absolute terms, one could predict 12 incident cases of hemorrhagic stroke per 10,000 patients chronically treated with aspirin (29). The ATT Collaboration reported a statistically significant 22% increased incidence of hemorrhagic stroke in patients on antiplatelet treatment (30).

**ASPIRIN FOR PRIMARY CVD PREVENTION IN DIABETES.** Patients with diabetes have a 2 to 4× greater risk of cardiovascular events than individuals of the same age and sex without diabetes (31,32). Data by Haffner

et al. (33) suggest that there is a similar risk of future CHD events for both diabetic subjects without prior CHD and nondiabetic subjects with previous CHD (33). However, a meta-analysis of 13 studies, involving 45,108 patients (34), showed that the cardiovascular risk of diabetic patients without previous CVD is significantly lower than that of nondiabetic patients with previous CVD (34). Three RCTs conducted specifically in patients with diabetes (16,18,35) and 6 RCTs in which patients with diabetes were trackable subgroups (1% to 22%) (10–15) failed to provide definitive results on the effect of aspirin in primary CVD prevention. A meta-analysis of these 9 RCTs found that aspirin was associated with statistically nonsignificant reductions of CHD events (−9%) and of cerebrovascular events (−11%) (31). Three other meta-analyses found similar estimates (36–38). Based on the overall negative results of these RCTs, it is generally assumed that aspirin is less effective in patients with diabetes than in individuals without diabetes. However, the individual patient-level meta-analysis by the ATT Collaboration showed that the effect of aspirin on major cardiovascular events was similar for participants with and without diabetes (risk ratios: 0.88 [95% confidence interval (CI): 0.67 to 1.15] and 0.87 [95% CI: 0.79 to 0.96], respectively) (6). The wider 95% CI for diabetes is attributable to its smaller representation (about 4,000 patients with diabetes vs. about 91,000 without diabetes) (6).

**NEW DATA ON ASPIRIN IN PREVENTION OF CANCER.** In the past 10 years, the notion of a favorable noncardiovascular effect of aspirin in preventing cancer-related mortality has progressively gained consensus. First observed for colorectal cancer, the effect was later reported for other malignancies, especially adenocarcinomas. In a meta-analysis by Rothwell et al. (39), 8 RCTs (not homogeneous as to the level of cardiovascular risk and aspirin doses [75 to 650 mg daily], in both primary and secondary CVD prevention) found that cumulative total mortality was 10.2% in aspirin users versus 11.1% in nonusers (odds ratio: 0.92, 95% CI: 0.85 to 1.00). The hazard ratio, which was calculated in a time-dependent analysis in 7 of the 8 trials, was 0.82, a significant total mortality reduction (95% CI: 0.70 to 0.95). Reduction in cancer mortality was a driving force for this, and became especially relevant after 5 years (hazard ratio: 0.66) and persisted even after 20 years for GI and other solid cancers (hazard ratio: 0.65). Regular, daily administration of aspirin for the entire trial duration appeared to be necessary to confer the benefit. These data were reinforced by another more recent meta-analysis of 11 RCTs, mainly of secondary CVD prevention with low-dose aspirin (75 to 325 mg daily), yielding a significant reduction in cancer mortality (risk ratio: 0.77, 95% CI: 0.63 to 0.95) (40). Similar results for cancer incidence were obtained by pooling 6 trials of primary CVD prevention (odds ratio: 0.76, 95% CI: 0.66 to 0.88) (41), and confirmed by data from the Women's Health Study (42).

**THE NET CLINICAL BENEFIT.** The net clinical benefit of giving aspirin to healthy individuals is made difficult to assess by the imprecision of estimates of benefits and risks, especially for rare events, such as intracranial hemorrhage, and by the difficulty of weighing ischemic versus bleeding events. A recent extensive systematic review of aspirin in primary prevention concludes that "there is a fine balance between benefits and risks from regular aspirin use in primary prevention of cardiovascular disease" (25). However, although the number of ischemic events averted (on average: 72 averted by treating 10,000 patients for 10 years) was similar to the number of major bleeding events incurred (on average: 47 events), aspirin use would be associated with about 40 deaths averted against an average of 9 hemorrhagic strokes incurred, with an apparent overall benefit (**Table 2**).

## CURRENT GUIDELINES

The 2012 ESC (7) and the American College of Chest Physicians (ACCP) (8) guidelines have addressed the issue of aspirin in primary CVD prevention with different conclusions. According to the ESC guidelines,

**TABLE 2 Number of Events Averted or Incurred Should 10,000 Persons Be Treated With Aspirin in Primary CVD Prevention and Followed-Up for 10 Years**

| | Range | Mean |
|---|---|---|
| Events averted | | |
| Deaths (any cause) | 33–46 | 39.5 |
| MCE (CV death, MI, or stroke) | 60–84 | 72.0 |
| Total CHD events | 47–64 | 55.5 |
| CRC deaths | 34–36 | 35.0 |
| Cancer deaths | 17–85 | 51.0 |
| Events incurred | | |
| Major bleeds | 46–48 | 47.0 |
| GI bleeds | 117–182 | 149.5 |
| Hemorrhagic strokes | 8–10 | 9.0 |

Table reprinted with permission from Sutcliffe et al. (25).
CHD = coronary heart disease; CRC = colorectal cancer; GI = gastrointestinal; MCE = major cardiovascular event(s); other abbreviations as in Table 1.

aspirin or clopidogrel "is not recommended in individuals without cardiovascular or cerebrovascular disease" due to the increased risk of major bleeding (Class III, Level of Evidence: B) (7). Conversely, the ACCP guidelines suggest low-dose aspirin 75 to 100 mg daily for persons age 50 years or older without symptomatic CVD (Grade 2B) (8), remarking that aspirin slightly reduces total mortality regardless of cardiovascular risk profile if taken over 10 years. In people at moderate-to-high risk of cardiovascular events, the reduction in MIs is closely balanced by an increase in major bleeds, prompting aspirin use in individuals who value preventing an MI substantially more than avoiding a GI bleed.

Concerning diabetes, the ACCP guidelines suggest that the relative benefit of aspirin is similar in patients with and without diabetes. The American Diabetes Association, the AHA, and the ACC (31) recommend as follows:

1. Primary cardiovascular prevention with aspirin is reasonable in diabetic patients whose 10-year risk of events is >10% (men age >50 years and women age >60 years with at least 1 additional risk factor: smoking, hypertension, dyslipidemia, albuminuria, or family history of premature cardiovascular events) and who are not at increased risk of bleeding (no history of gastrointestinal bleeding or peptic ulcer disease, no concurrent use of other medications that increase bleeding risk).
2. Aspirin should not be recommended in diabetes patients at low risk of cardiovascular events, because the potential adverse effects from bleeding offset the potential benefits.
3. Aspirin may be considered for diabetes patients at intermediate risk of cardiovascular events (younger patients with at least 1 risk factor, older patients with no risk factors, or patients with a 10-year risk of 5% to 10%).

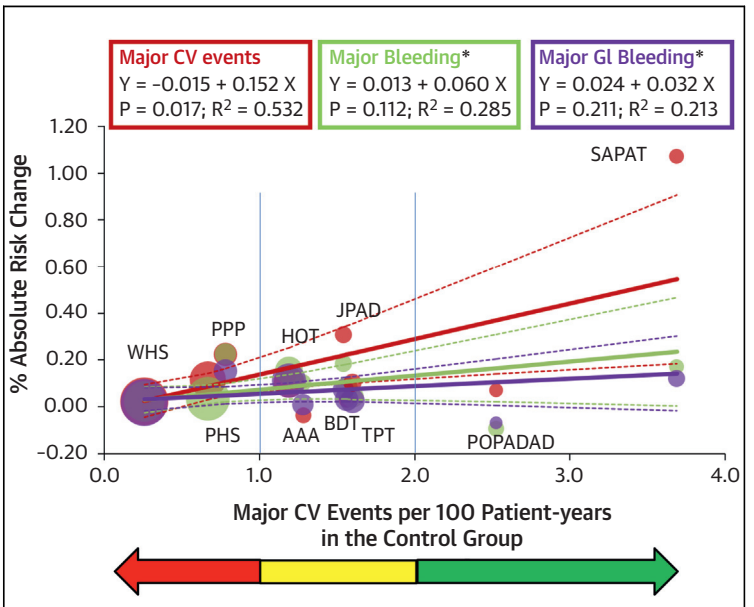



**FIGURE 1 Relationships Between Magnitude of Antithrombotic Benefit and of Bleeding Risk Connected With the Use of Aspirin, and Absolute Cardiovascular Risk, in Various Subsets of Subjects in Primary Prevention**

To examine the strength of the association between treatment effects of aspirin on cardiovascular events, major gastrointestinal bleeding, and total major bleeding with the level of cardiovascular risk per 100 person-years in the control arm of the trials, we fitted univariate inverse variance-weighted linear regressions of the risk difference for the outcome events per 100 person-years between the 2 experimental arms of each study as a dependent variable against the aforementioned explanatory variable. The **size of circles** is proportional to the inverse of variance of the risk difference. **Red arrow** denotes the area where benefit likely equals risk, **yellow area** denotes area of prescription uncertainty, and **green arrow** denotes the area where benefit most likely exceeds risk. **Continuous line** = linear regression; **dotted line** = lower and higher 95% confidence interval (CI). Trials included: U.S. PHS (Physicians Health Study) (13), BDT (British Doctors Trial) (10), TPT (Thrombosis Prevention Trial) (14), HOT (Hypertension Optimal Treatment) study (15), PPP (Primary Prevention Project) (12), Women's Health Study (11), POPADAD study (Prevention of Progression of Arterial Disease and Diabetes) (18), JPAD study (16), and the AAA (Aspirin for Asymptomatic Atherosclerosis) trial (17). Data from the Swedish Angina Pectoris Aspirin Trial also are included (47). Further details can be found in the Online Appendix.
ASA = acetylsalicylic acid (aspirin); CV = cardiovascular; GI = gastrointestinal.

## ONGOING STUDIES

For information regarding ongoing studies, please see Online Table 2. Most aspirin trials for primary CVD prevention have enrolled individuals at low cardiovascular risk, with estimated coronary event rates <1% per person-years. To fill a missing gap, 5 ongoing RCTs are investigating the safety and efficacy of 100 mg aspirin daily versus placebo (or vs. no aspirin) in more than 60,000 men and women at a higher level of cardiovascular risk, that is, without known CVD but with estimated rates of coronary events of 1% to 2% per person-years (or of total cardiovascular events ~3% per person-years). In all 5 RCTs, the primary efficacy outcome includes vascular death, nonfatal MI, and nonfatal stroke to be weighed against major bleeding (mainly GI and intracranial) and other adverse events. The duration of follow-up is 4 to 7.5 years or driven by the number of accrued events. The enrolled populations range from nondiabetic subjects with ≥2 or ≥3 risk factors, to elderly patients age ≥70 years (43), elderly (age 60 to 85 years) with additional risk factors (44), and individuals with diabetes (ASCEND: A Study of Cardiovascular Events iN Diabetes; NCT00135226) or with diabetes taking a statin (45). ENVIS-ion (Aspirin for the Prevention of Cognitive Decline in the Elderly: A Neuro-Vascular Imaging Study) is a substudy of the ASPREE (Aspirin in

**TABLE 3 Arguments for and Against the Use of Aspirin in Primary Prevention**

| Contra | Pro |
|---|---|
| Bleeds induced numerically equal ischemic events prevented. | Although this may be true in some of the primary prevention studies, this is unlikely to hold for high-risk primary prevention, in which no data are so far available and projections (Fig. 1) would indicate an NNH higher than the NNT. |
| Bleeds induced have a similar prognostic implication as ischemic events averted. | This is, with the exception of the rare occurrence of intracranial hemorrhage (approximately one-fifth of all major bleeds), unlikely to be true, as nonfatal ischemic events averted are mostly "spontaneous" myocardial infarctions and (ischemic) strokes. |
| | Patients' preferences: most patients would prefer nonfatal major bleeding to a nonfatal myocardial infarction or stroke. |
| | Aspirin may reduce the risk of cancer in the long-term, extending the benefit beyond CVD prevention, and so far is underestimated in the relatively short follow-up of CVD prevention studies. |
| Risk estimates based on relatively old charts or algorithms (e.g., the Framingham Risk Score, or the European Society of Cardiology SCORE) may overestimate the current risk of CVD. | This is an unavoidable limitation of all analyses based on risk calculations. The effect is likely—in any case—to be minor. |

CVD = cardiovascular disease; NNH = number needed to harm; NNT = number needed to treat; SCORE = Systematic Coronary Risk Evaluation.

Reducing Events in the Elderly) study, investigating the effects of aspirin versus placebo on brain lesions assessed by magnetic resonance imaging after 3 years of treatment (46).

**TAILORING THERAPY ACCORDING TO BASELINE RISK IS STILL THE BEST CURRENT PRACTICAL GUIDANCE.** In primary CVD prevention, where the risk of developing atherothrombotic events for each individual patient is generally low, it is essential to estimate the individual baseline risk of such events and to carefully balance this against the side effects of therapy, in this case bleeding. Cardiovascular risk can be viewed as a continuum, increasing from primary prevention in young totally healthy individuals, to high-risk primary prevention, and then to secondary prevention (**Fig. 1**). There is indeed no theoretical reason or any evidence suggesting a discontinuity of aspirin effects throughout these categories. The benefit of treatment (saving major cardiovascular events) is clearly superior to the risk (inducing major bleeding) in the setting of secondary cardiovascular prevention. In the lowest risk category of secondary prevention, the stable angina population investigated in the Swedish Angina Pectoris Aspirin Trial (47), the use of aspirin 75 mg/day was associated with a significant 32% reduction in vascular events, a 35% increase in major bleeding, and 9 versus 5 fatal bleeds in the aspirin and placebo groups, respectively, and was judged to be clearly favorable, with 118 vascular events prevented versus 10 patients lost through fatal bleeds for 10,000 patient-years of treatment (47).

It is hard to imagine that, going down the spectrum of cardiovascular risk from secondary to primary prevention, there would be an immediate drop of the risk/benefit ratio making aspirin use suddenly unappealing. Nature usually does not make jumps. Indeed, a graphical evaluation of the benefit-risk balance, as portrayed in **Figure 1**, indicates a large area of cardiovascular risk in primary prevention where data from trials are lacking, but in whom the benefit may still outweigh the risk. The ongoing trials will try to answer this question. In the meantime, however, taking into account the logical argument of the continuum in primary and secondary prevention, the argument raised that for the entire primary prevention "the balance between vascular events avoided and major bleeds caused by aspirin is substantially uncertain because the risks without aspirin, and hence the absolute benefits of antiplatelet prophylaxis, are at least an order of magnitude lower than in secondary prevention" (48) should not be raised generically.

Additional considerations (**Table 3**) mostly prompt aspirin use in primary prevention. Particularly worthy of additional discussion are the following:

1. Most models attribute equal weight in terms of patient preference to a nonfatal cardiovascular event (MI and ischemic stroke) and to major bleeding. With the exception of the rare occurrence of hemorrhagic stroke, this is hard to concede. Although not at all negligible in terms of consequences for deaths and disabilities (49), the risk of hemorrhagic stroke appears to be around one-fifth of all major bleeding events incurred because of aspirin use (Online Table 1), and its fatal consequences are already comprised in total deaths estimates associated with aspirin use, which points toward a net benefit (25).
2. The alleged sex differences, proposed for the aspirin-related protection from cardiovascular events (11), do not seem to hold when the entire evidence is reviewed and analyzed (6).

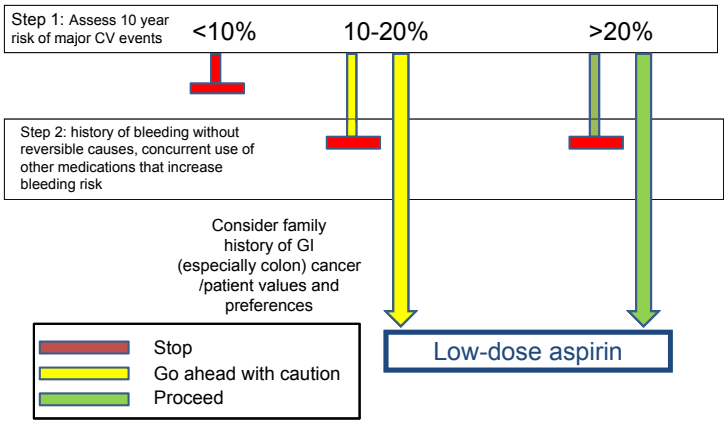
It is, however, probable that risk scores developed some years ago do not reflect—and likely overestimate—the current situation of cardiovascular risk, which has decreased over time for a variety of reasons, including the implementation of effective prevention strategies, such as lifestyle measures, statins, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers. These treatments target atherothrombosis upstream of thrombosis-related events, and therefore, compress part of the

aspirin benefit. Such an argument has been raised to recommend these nonantithrombotic treatments as alternative to, rather than complementary to aspirin (6). We argue, however, that there are still categories for individuals in primary prevention featuring the level of risk above a certain threshold, and in these a substantial number of major cardiovascular events are likely to be preventable by aspirin with a reasonable efficacy/safety balance.

**DEFINING THE THRESHOLD.** Thus, we should identify a threshold risk level above which recommending aspirin is expected to produce more benefit than risk. We propose such a threshold at a risk of major cardiovascular events (death, MI, and stroke) ≥2 per 100 patient-years, assessed through the most accurate and country-specific risk factor estimates. Such a proposal is: 1) logically derived from the previously-described evidence; and 2) a conservative one, privileging safety rather than efficacy. Upon inspection of **Figure 1**, one could argue that the lines depicting the risk-level dependence of benefit and risk diverge even earlier than the 2 per 100 patient-years level. However, there are wide confidence intervals of such estimates. Therefore, an "uncertainty area" should be indicated, at risk levels between 1 and 2 per 100 patient-years, in which the decision to prescribe or not to prescribe aspirin is left to the physician's discretion and to the patient's preferences (**Central Illustration**).

The general principles upon which such a proposal is drawn are shared by several other groups (8,31), although threshold levels for recommendation vary. Our proposed threshold level is higher, and therefore, more conservative than that proposed by the U.S. Preventive Task Force (50) (0.6 per 100 patient-years) and suggested by the AHA (≥1 per 100 patient-years) (51). It is also significantly higher than the current recommendation from the ACCP (8), which suggests low-dose aspirin daily for all persons age ≥50 years without symptomatic CVD. The proposed threshold risk level of 2 major cardiovascular events/100 patient-years, corresponding approximately to a SCORE risk of 7% to 10% at 10 years (6,8), is sufficiently conservative to allow a net cardiovascular benefit to be achieved. The reported benefit of aspirin in also preventing noncardiovascular deaths in the long term, such as death due to cancer, can only reinforce such recommendations while waiting for definite proof-of-concept through the completion of properly-designed clinical trials.

Beyond routine screenings, we also recommend that additional evidence of risk can be used to prompt doctors and patients to adopt antithrombotic therapy with aspirin in conditions of indecision (52). We also recommend that, after careful transferring of the relevant information to patients, individual values and preferences should be taken into account.




**CENTRAL ILLUSTRATION A Proposed Practical Stepwise Approach to the Use of Aspirin in Primary CV Prevention**

The first step should be an assessment of patient's eligibility to the treatment, by assessing the 10-year risk of major cardiovascular (CV) events (death, myocardial infarction, and stroke), according to local population risk estimates. Eligible patients will be those with an estimated 10-year risk >20%. Patients with a 10-year risk between 10% and 20% will be deemed as "potentially eligible," and those with a risk <10% will be considered noneligible. The second step will be assessing safety in eligible and potentially-eligible patients, through a history of bleeding without reversible causes, and concurrent use of other medications that increase bleeding risk. In the absence of such conditions, patients with a risk >20% should be given low-dose aspirin, and those with a risk 10% to 20% should be engaged in a case-by-case discussion, factoring family history of gastrointestinal cancer (especially colon cancer) and patient values and preferences; particularly motivated patients can then be prescribed low-dose aspirin.

We recognize that across the entire area of high cardiovascular risk in primary prevention, and especially in high-risk primary prevention (≥2 major cardiovascular events per 100 patient-years) (**Fig. 1**), it is opportune to acquire more data through other placebo-controlled trials, some of which are already ongoing. Particularly problematic areas include diabetic patients or patients with asymptomatic PAD. The mere presence of either does not appear sufficient for aspirin to confer a benefit clearly exceeding the risk.

## CONCLUSIONS AND RECOMMENDATIONS

We recommend that aspirin use in the primary prevention of acute MI and other atherothrombotic cardiovascular events in subjects of both sexes is guided by an assessment of the underlying cardiovascular risk (Grade of Recommendation: I, Level of Evidence: B) (**Central Illustration**). We suggest that

aspirin be considered in the primary prevention of CVD in both sexes at a level of risk of major cardiovascular events (death, MI, and stroke) >2 per 100 subject-years, provided they have no clear evidence of increased risk of bleeding (GI bleeding or peptic ulcer disease, no concurrent use of other medications that increase bleeding risk) (Class of Recommendation: IIa, Level of Evidence: B).

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**KEY WORDS** aspirin, bleeding, cancer, death, myocardial infarction, primary prevention

**APPENDIX** For supplemental material and tables, please see the online version of this article.